**BMJ Comment**

**Title:**

**Diagnostic tests for COVID-19 – improving accuracy and global harmonization**

**Authors**:

**Jim Huggett1, Kathryn Harris2, Timothy D McHugh3, Jacob Moran-Gilad4, Alimuddin Zumla5**

**Institutional affiliations**:

**1** School of Biosciences & Medicine, Faculty of Health & Medical Sciences, University of Surrey and National Measurement Laboratory at LGC, Queens Road, Teddington, United Kingdom

2 Microbiology Department, Great Ormond Street Hospital NHS Foundation Trust, London, UK.

3 Center for Clinical Microbiology, Division of Infection and Immunity, University College London, United Kingdom

4 Department of Health Systems Management, School of Public Health, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel

**5** Center for Clinical Microbiology, Division of Infection and Immunity, University College London, and National Institutes of Health and Research Biomedical Research Centre, University College London Hospitals NHS Foundation Trust, London, UK.

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**Corresponding author**: Dr Jim Huggett PhD.FRCP

School of Biosciences & Medicine, Faculty of Health & Medical Sciences, University of Surrey and National Measurement Laboratory at LGC, Queens Road, Teddington, United Kingdom Email: j.huggett@surrey.ac.uk

As the epidemic outbreaks of novel respiratory tract infectious diseases SARS, MERS and the ongoing pandemic of the novel coronavirus-2019 COVID-19 have shown, the development of accurate diagnostic tests play an important role in outbreak management1 2. Whilst serological tests are cheap and practical to use, providing rapid point-of-care tools for screening and diagnosis, they require further confirmatory tests. In addition, there is a lag period of 5 to 14 days for virus-specific IgM antibodies to appear after infection. By comparison, molecular based assays targeting the viral genome are more specific and as such more relevant for rapid detection of new pathogens. SARS-CoV-2 is an RNA virus and so most molecular assays are based on reverse transcriptase quantitative PCR (RT-qPCR), although alternative amplification chemistries are also being used. The unprecedented pace with which the scientific community has responded to, and collaborated together on, COVID-19 pandemic3 is reflected by the rapid development, roll out of in-house laboratory developed tests and subsequently high throughput commercial diagnostic solutions 4 5. Without bespoke in-house laboratory solutions it is difficult to envisage how the world could have responded so quickly to detect and manage patients and begin to identify clinical and epidemiological characteristics of the COVID-19 pandemic.

Rapidly developed in-house PCR based assays play a fundamental role in identification of new diseases which are not catered for by available commercial diagnostic platforms that currently underpin health service laboratories. They also serve as a reference for confirmation of results from other assays and as a backup where supply of commercial tests is disrupted, for example the reagent shortages reported for the current platforms for SARS-CoV-2 detection. Furthermore, pricing structures for commercial platforms may render them unaffordable in low resource settings. PCR provides the ability to design, validate and roll out assays targeting any sequence of interest at very short notice. For these reasons, PCR tests are currently playing a crucial role in identifying SARS-CoV-2 infected patients. However, some key questions remain on the accuracy of these diagnostic tests for identifying and confirming new cases, guiding clinical management, infection control, disease surveillance, patient discharge and follow up. In-house assays differ from commercially available tests because they are often applied using ‘research use only’ reagents without the quality assurance required for the mass production and use of commercial assays. Thus, ensuring optimal diagnostic performance and traceability, to account for discrepant results between laboratories, is more challenging for the in-house setting.

A range of COVID-19 molecular assays are currently being used on a globally, by multiple laboratories, of varying quality and expertise. Fundamental to RT-qPCR is the selection of primers and molecular probes, the combination of which are referred to as panels, and these make the major contribution to the assay characteristics. The WHO highlights seven different assay panels6 and selection of a test is complicated by the availability of an increasing number (currently over 500) commercial tests which are being marketed7. Whilst the pace of test adoption reflects the urgent global response to the COVID-19 pandemic, it is crucial that accurate assessment of diagnostic performance of each assay is monitored. The importance of quality systems for diagnostics cannot be overstated, since the systems required (such as reference materials) to ensure test quality are challenging to implement on a timeline comparable to the assays they need to support, and thus are lagging behind.

Currently recommended assays4 6 detect different regions of the SARS-CoV-2 viral genome. Whilst this can provide resilience by accounting for sequence variation between populations, it can also lead to diagnostic discrepancies associated with genomic variability or analytical performance. Often overlooked are the pre-analytical steps of the recommended protocols, these include specimen sampling, storage, processing and preparation required prior to amplification, as well selection and use of internal and external controls and guidelines for standardisation approaches for these are required. The potential impact is well known. When using non-standardised tests for viral load testing, differences in excess of a hundred-fold are not uncommon8 , an artificially low signal (e.g. due to poor sample processing) can manifest as a false negative result.

Whilst the world approaches a million tests using tests for detecting SARS-CoV-2, it becomes important that national and global public health actors and regulatory bodies take forward solutions to support quality control for COVID-19 testing. *First*, the quality systems which assist the rapid development and confident application of diagnostic PCRs should be an integral part of a global emergency response planning including access to reference materials and biobanked clinical samples for test validation. *Second*, standardised generic protocols and standards to assist with test quality, which could then be adapted to specific scenarios, would better prepare the world for pandemics and the diagnostic testing component of the response. The molecular standards community are already working on solutions; systems more common to clinical chemistry, which combine high accuracy measurements and well characterized reference materials, are increasingly available to support harmonization of molecular diagnostic procedures 9 10. *Third*, molecular diagnostic methods such as digital PCR are improving and offer increasingly accurate and robust diagnostic approaches. 11 12 These simplify the routes to ensure traceability, evaluate test performance and increase confidence in the result providing reliable detection. The uncertainty of test reliability in the COVID-19 pandemic has highlighted the imperative of standardisation in diagnostic test development, it must be part and parcel of the global response, not only for the current pandemic but also setting a precedent for novel emerging pathogens.

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